REMARKS

The examiner's prior art rejections, it is respectfully submitted, should be withdrawn.

The examiner admits that June does not disclose human antibodies against human CD28. The examiner also admits that the antibodies which are produced by June do not directly activate human T lymphocytes. However, the examiner maintains that, nevertheless, it would be obvious to produce antibodies having such features. The argument is based on the disclosure of Tacke. The examiner alleges that the latter reference teaches rat antibodies to rat CD28. (The statement to the contrary on line 3 of page 5 of the office action is clearly an inadvertent misstatement in view of the other correct statements made on the same page.) The examiner also alleges that Tacke discloses that its antibodies do directly stimulate T cells without occupancy of the T cell receptor and that they are produced "using immunization strategies based on transfected cells lines rather than T cells." The examiner alleges that June also did or could have used such transfected cell lines. Consequently, the examiner concludes that there would have been a reasonable expectation that directly stimulating antibodies specific for human CD28 were in fact or could have been produced by June. It is respectfully submitted that this line of reasoning is insufficient to support a rejection under 35 USC § 103(a).

The examiner seems to be saying that, although June itself did not recognize the production of any directly stimulating antibodies, they might have been there anyway because of what Tacke's experiments showed. In essence, the examiner is stating that Tacke makes it obvious to try to find directly stimulating antibodies among those produced in the June experiments. Maybe they are there, maybe they are not, according to the examiner. However, this has long been held to be an insufficient basis for an obviousness rejection. See, e.g., *In re Tomlinson*, 363 F.2d 928, 150 USPQ 623 (CCPA 1966). The same defect exists in the examiner's other line of reasoning, i.e., if it turns out that June did not in fact produce the sought antibodies, then June could somehow produce them, presumably by somehow modifying its experiments. This is an even worse case scenario of the obvious to try doctrine and is even more insufficient to support a rejection. The examiner does not even allege how June might have modified his experiments to arrive at the claimed subject matter. Clearly, this is an insufficient basis for an obviousness rejection.

In essence, the examiner seems to be saying that perhaps inherently June produced antibodies which were directly stimulating. Whereas inherency may have some sway in an anticipation situation (which this clearly is not), it is irrelevant in the obviousness rejection being made here. Furthermore, the examiner has not provided a showing of any motivation to modify either June or Tacke in a way required to arrive at antibodies having all of the characteristics required by the claims of this application. Thus, this rejection must be withdrawn.

The same is true for the rejection based on Siefken.

Reference is made to Example 3 of this application wherein, in the second paragraph, Siefken et al. is discussed and it is concluded that the invention is "unlike" the Siefken et al. results in that "it is not necessary to crosslink [the invention's antibodies] artificially by means of a second antibody." See the "results" paragraph bridging pages 60 and 61 of Siefken et al. Furthermore, Siefken et al antibodies are able to stimulate only a minor T cell subset, $CD4^{+}CD45RO^{+}$. Clearly, humanization of such an antibody cannot lead to the antibody claimed in this invention.

The foregoing amendments respond to certain of the Examiner's linguistic comments. It is respectfully submitted that the original versions of the claims are otherwise perfectly fine under the statute. Nevertheless, the examiner's close attention to detail is sincerely appreciated. The expression "in this way" has not been modified because applicants feel that in context it is clear which "way" is intended. Plural entities make perfect sense when biological molecules are involved, such as antibodies, cells, etc.

As for other clarification of the claims, the "direct" aspect is supported explicitly, e.g., on page 3, line 6 from the bottom. The last line added to claim 3 is supported, e.g., at page 5, beginning of the second paragraph.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend the claims as follows:

1. (Amended) [Human-compatible] A human-compatible monoclonal [antibodies] antibody which [are] is specific for human-CD28 and [activate] activates human T-lymphocytes of several to all sub-groups without occupancy of an antigen receptor of the human T-lymphocytes and thus antigen-non-specifically, and which is effective for treating a disease with pathologically reduced number of CD4 T-cells or an autoimmune disease.